Growth Mixture Models

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Outline

- Motivating Example: The ADAPT trial
- Two Options for Modeling Heterogeneity
  1. Mixed Effects/Growth Curve Models
  2. Growth Mixture Models
- Comparison of Options & Final Thoughts

AD and Inflammation

- AD characterized by β-amyloid plaques and neurofibrillary tangles
- AD is progressive, with a long pre-clinical period.
- Inflammatory processes have been linked to plaque and tangle formation
- Inflammatory processes also linked to clearance of β-amyloid.

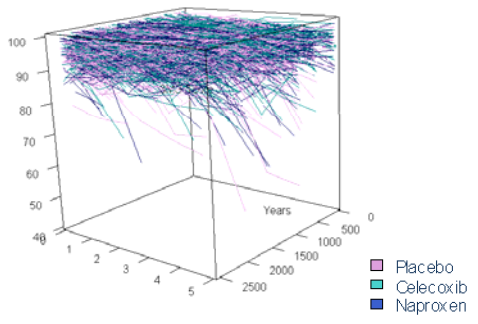
AD and NSAIDs

- In observational studies, NSAID use associated with reduced risk of AD
- AD treatment trials show no effect of NSAIDs
- In an MCI prevention trial, NSAID increased risk.

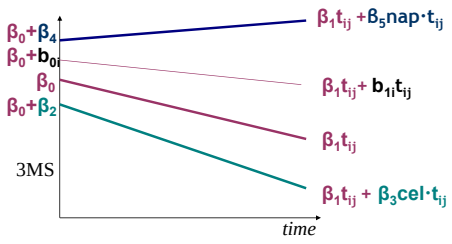
The ADAPT Trial

- Multi-site prevention trial N=2528
- Participants 70+, family history of AD
- 200 mg of celecoxib bid, 220 mg of naproxen sodium bid, or matching placebo (1:1:1.5)
- Enrollment began in 2001, halted December 2004 due to safety concerns.
- Study cohort is still being followed.

ADAPT 3MS Total

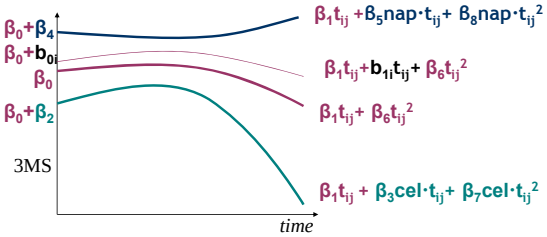


Option 1. Mixed Effects Model



$$Y_{ij}=\beta_0+b_{0i}+\beta_1 t_{ij}+b_{1i} t_{ij}+\beta_2 cel+\beta_3 cel \cdot t_{ij}+\beta_4 nap+\beta_5 nap \cdot t_{ij}+\varepsilon_{ij}$$

Mixed Effects with Quadratic Term

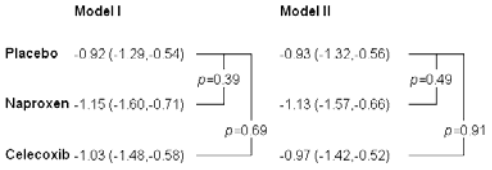


$$Y_{ij}=\beta_0+b_{0i}+\beta_1 t_{ij}+b_{1i} t_{ij}+\beta_2 cel+\beta_3 cel \cdot t_{ij}+\beta_4 nap+\beta_5 nap \cdot t_{ij}+\beta_6 t_{ij}^2+\beta_7 cel \cdot t_{ij}^2+\beta_8 nap \cdot t_{ij}^2+\varepsilon_{ij}$$

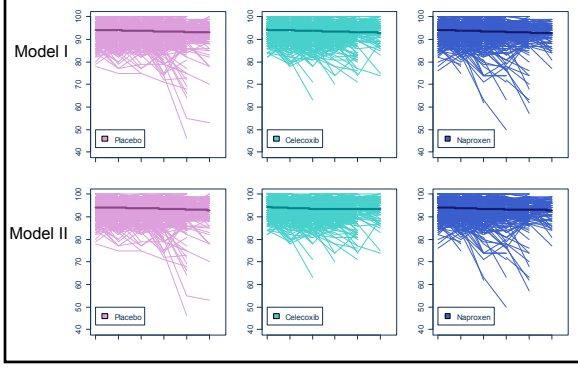
Parameter Estimates

Coefficient	Model I	Model II
β_0	94.24 (0.11)	94.20 (0.12)
$\beta_1 t_{ij}$	-0.23 (0.05)	-0.14 (0.10)
$\beta_6 t_{ij}^2$		-0.02 (0.02)
$\beta_2 cel$	0.05 (0.16)	0.20 (0.17)
$\beta_3 cel \cdot t_{ij}$	-0.03 (0.07)	-0.39 (0.14)
$\beta_7 cel \cdot t_{ij}^2$		0.09 (0.03)
$\beta_4 nap$	-0.04 (0.16)	0.05 (0.17)
$\beta_5 nap \cdot t_{ij}$	-0.06 (0.07)	-0.26 (0.15)
$\beta_8 nap \cdot t_{ij}^2$		0.05 (0.03)
Residual Variance	5.96 (0.12)	5.95 (0.12)
Intercept Variance	6.21 (0.31)	6.22 (0.31)
Slope Variance	0.75 (0.05)	0.75 (0.05)
Intercept, Slope Covariance	0.51 (0.10)	0.51 (0.10)
Log Likelihood (Parameters)	-24520.101 (14)*	-24514.994 (19)
** Note: models also control for age and APOE genotype*		

Expected Change Over 4 Years

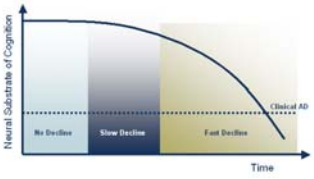


Observed and Predicted Trajectories



Rates of Decline in Pre-Clinical AD

- Prior to clinical dx, decline rate not constant
- Can consider trajectories as being in "classes": no, slow, & fast decline.



The Timing Hypothesis

- Contradiction between observational and clinical trials due to differences in timing of exposure to NSAIDs
- Early/little or no decline: NSAIDs good
- Later/ substantial decline: NSAIDs bad
- Observational trials: most individuals in no/slow decline class when exposed
- Clinical trials: larger proportion of individuals in the fast decline class

Testing the Timing Hypothesis

- Ideal: Stratify individuals by decline class, fit mixed effects models with NSAID effects separately for each class.
- Problem: we don't know for sure how many classes there are, or who is in each class. Class is a *latent* variable.

The Meaning of *Latent*

Dictionary.com:

- Normal Usage: present but not visible, apparent, or actualized; existing as potential: latent ability.
- Pathology: (of an infectious agent or disease) remaining in an inactive or hidden phase; dormant.

Latent Variables in Biostatistics

- "concepts in their purest form" "unmeasured or unobserved" (*Bollen, 1989, p.11)*
- "in principle or practice, cannot be observed" *(Bartholomew, 1996, p. 12)*
- "Underlying: not directly measurable. Existing in hidden form but usually capable of being measured indirectly by observables" *(Bandeen-Roche, 2006)*

Reasons for Modeling with Latent Variables

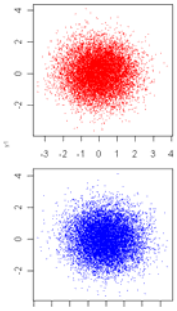
- NIH wants me to be sophisticated
- Acknowledge, study issues with measurement; *correct attenuation*; etc.
- Reveal underlying truth (e.g. "discover" latent types)
- The complexity of my problem demands it
- Needed to operationalize and test theory

Mixed Effects Models as "Growth Models"

- Term used in developmental research
- "Growth" – getting taller, smarter, etc.
- Fixed effects (intercept, slope, quadratic) referred to as "Growth Factors"

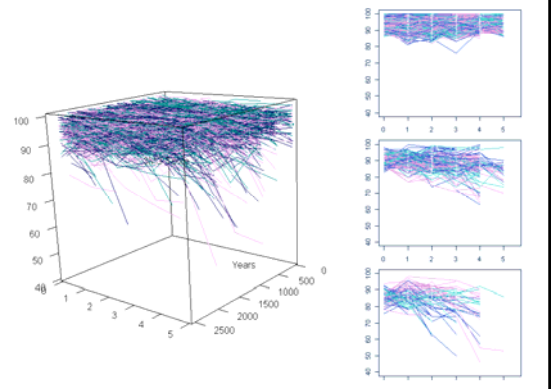
Mixture Models

- Useful when you believe your population is actually a *mixture* of subpopulations.
- "Mixture" here has nothing to do with "Mixed Effects"



Option 2. Growth Mixture Models

- Allows for the estimation of a pre-specified number of latent classes of trajectories
  - Determined via a combination of substantive theory, fit indices, and bootstrapped likelihood ratio tests.
- Estimates mixed effects model (growth model) parameters for each latent class



Growth Mixture Model Parameters

- For each class (indexed by *k*), we now have

$$Y_{ij}=\beta_{0k}+b_{0i}+\beta_{1k}t_{ij}+b_{1i}t_{ij}+\beta_{2k}cel+\beta_{3k}cel\cdot t_{ij}+\beta_{4k}nap+\beta_{5k}nap\cdot t_{ij}+\varepsilon_{ij}$$

- Simultaneously, model probability of membership in each class via multinomial logistic regression - this allows for inclusion of predictors of class membership (e.g., age, such that older individuals have greater probability of membership in the fast-decline class.

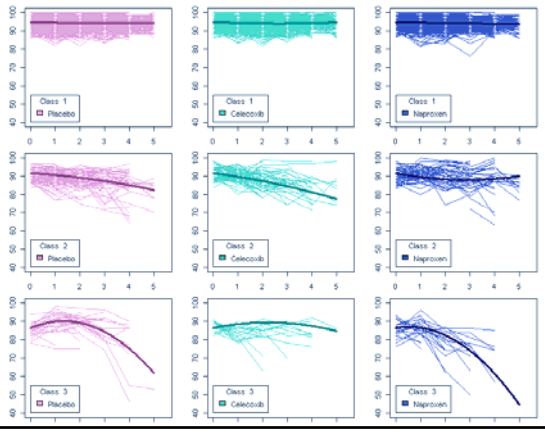
Fitting Growth Mixture Models

- Need specialized software (MPLUS, OpenMx)
- Entails the estimation of a large number of parameters
- Computationally intensive

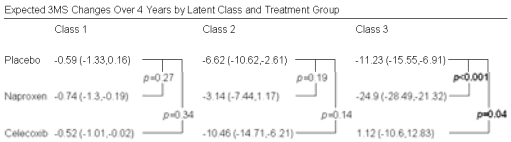
Growth Mixture Model Parameter Estimates

	1-Class Model	3-Class Model		
Class Probability	**100%**	**86%**	**10%**	**4%**
β_0	94.20 (0.12)	94.73 (0.08)	91.70 (0.27)	86.31 (0.28)
$\beta_1 t_{ij}$	-0.14 (0.10)	-0.32 (0.09)	-0.84 (0.53)	5.63 (0.81)
$\beta_6 t_{ij}^2$	-0.02 (0.02)	0.04 (0.02)	-0.20 (0.07)	-2.11 (0.11)
$\beta_2 cel$	0.20 (0.17)			
$\beta_3 cel \cdot t_{ij}$	-0.39 (0.14)	-0.20 (0.13)	-0.88 (0.68)	-2.87 (1.64)
$\beta_7 cel \cdot t_{ij}^2$	0.09 (0.03)	0.06 (0.03)	-0.02 (0.11)	1.49 (0.25)
$\beta_4 nap$	0.05 (0.17)			
$\beta_5 nap \cdot t_{ij}$	-0.26 (0.15)	0.05 (0.14)	-1.73 (0.75)	-3.30 (0.97)
$\beta_8 nap \cdot t_{ij}^2$	0.05 (0.03)	-0.02 (0.03)	0.65 (0.10)	-0.03 (0.19)
Residual Variance	5.95	5.40		
Intercept Variance	6.22	4.76		
Slope Variance	0.75	5.56		

** Note: models also include age and APOE genotype*



Expected Change Over Time



A model where drug effects are forced to be the same across classes fits the data significantly worse (-2LLD: 369.23; $p<0.001$)

Comparison of Options

Mixed Effects

- Assumes one population
- Simpler interpretation
- More parsimonious
- Standard software
- Results can be more definitive

Growth Mixture Model

- Models subpopulations
- Complex interpretation
- More parameters
- Need larger sample
- Need $pecial $oftware
- Results not definitive; post-hoc subgroup analysis

Final Thoughts on Growth Mixture Models

- What does it all mean?
- possible to get fit indices, etc which support a multi-class mixture when really there are no underlying subgroups.
- Entails a number of assumptions about the within-person correlation and random effects, results can be *highly* sensitive to those assumptions
- Assumptions/model fit difficult to check
- Hypothesis generating/refining rather than confirming.